## REMARKS

### I. Introduction

In response to the Final Office Action dated January 12, 2009, claim 1 has been amended. Claims 1-8 remain in the application. Reconsideration of the application, as amended, including withdrawn claims 3 and 4, is requested.

### II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and were not required for purposes of patentability.

Claim 1 has been amended to clarify that the "low dose DRD2 binding atypical antipsychotics" are "low DRD2 binding", to be consistent with the definition provided in the specification at page 5, lines 11-16, which states that "low binding" antipsychotics are often referred to in the art as "atypical" antipsychotics. Likewise, claim 1 has also been amended to clarify that an A1- genotype is indicative of a candidate for treatment with "high dose or high binding DRD2 binding" antipsychotics, to be consistent with the definitions at page 4, line 19, to page 5, line 4, of the specification, and also with the doses and binding affinities of the antipsychotics used in the working examples of the specification.

### III. Examiner's Interview Summary

Record is made of a telephonic interview between Applicants' attorney, Karen Canady, and Examiner Lundgren held on July 15, 2009, in connection with the present patent application. The discussion during this interview centered on support in the specification for the claims as amended under PCT Article 19 during the international phase of this application. Per the Examiner's suggestion, Applicants have submitted a more detailed explanation of the support in the specification, including clarification of the significance of the data presented in Table 1 and the meaning of "CPZEK", a term used in the art for comparing doses of antipsychotic drugs. Applicants present the following arguments, reasoning and information in a good faith effort to advance prosecution. Should the Examiner require further clarification or identify further issues to be resolved, the courtesy of a telephone call to Applicants' attorney would be most appreciated.

## IV. Non-Art Rejection

On pages 2-4 of the Office Action, the Examiner rejected claims 1, 2, 5, 6, and newly added claims 7 and 8 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement for containing new matter. The Applicants traverse this rejection for the reasons set forth below. Reconsideration is respectfully requested.

### Problems With Antipsychotic Medications

As explained in the Background of the Invention at page 1 of the specification, the treatment of patients with antipsychotic medications is hindered by side-effects and complications that cause considerable distress and result in low adherence to medications. Older, "typical" antipsychotics bind tightly to the D2 dopamine receptor (DRD2) and some patients experience poor response to treatment with these medications. Currently used medications, known as atypical antipsychotics, bind to the D2 dopamine receptor with varying strength. While the atypical medications represent a significant advance in the treatment of psychosis, there are no guidelines to match patients to medication type to both maximize clinical response and to minimize the likelihood of harmful adverse effects, such as extrapyramidal movement symptoms and diabetes. Similarly, response to the class of antidepressant medications known as selective serotonin reuptake inhibitors (SSRI) has been variable. SSRIs are an effective treatment for a wide variety of psychiatric disorders for many patients, but some patients do not respond to medication. The invention addresses a need for predictors of patient response to assist clinicians in the selection of antidepressant as well as antipsychotic medications.

As discussed at page 4, lines 8-14 of the specification, the claimed invention is based on the discovery that Taq1A allelic status is associated with response to medications that act at the D2 dopamine receptor (DRD2) as well as response to selective serotonin reuptake inhibitors (SSRIs). By allowing clinicians to maximize response to treatment while minimizing the likelihood of adverse side effects based on Taq1A allelic status, the invention provides an advance in the treatment of patients with psychiatric disorders such as psychosis and depression.

During the telephonic interview of July 15, 2009, referenced above, the Examiner requested clarification as to how the data presented in the specification support the method as claimed as well as clarification of "typical" versus "atypical" antipsychotics, and the meaning of

"CPZEK" in the context of high dose and low dose treatment referenced in the claims. One question, regarding "therapeutic levels" of prolactin in connection with Table 1 of the specification, suggests there may be a misunderstanding about the significance of the data regarding prolactin levels. The objective addressed by the invention, with regards to prolactin levels, is to avoid adverse side effects of antipsychotic medications, such as hyperprolactinemia. This aspect, and others, of the invention were explained in the Amendment dated October 6, 2008, in a summary of the information one skilled in the art would glean from the data presented in the specification, and are repeated below (with further clarifications added):

**Significance of Prolactin Levels**

"Hyperprolactinemia has been considered an inevitable consequence of treatment with any typical antipsychotic agent." (See carryover paragraph 0048, at pages 15-16 of the specification.) As is known in the art, antipsychotics "vary widely in their binding affinity for the D2 receptor" (para. 0049, at p. 16, l. 3). Some atypical antipsychotics, such as Clozapine and Quetiapine have a lower D2 binding affinity than dopamine and are not associated with hyperprolactinemia. Hyperprolactinemia is more commonly associated with tighter binding agents such as Risperidone and typical antipsychotics. (See remainder of para. 0049, which also provides literature citations.) Thus, the class of antipsychotics known as "typical" antipsychotic agents are known to be tight binders of the D2 receptor and associated with hyperprolactinemia. The "atypical" antipsychotic agents vary in their D2 binding affinity, from loose binders (Clozapine) to tighter binders (Risperidone). Prolactin levels observed, however, are not an accurate reflection of drug D2 occupancy (see discussion of Risperidone and Olanzapine as giving comparable D2 drug occupancy levels but differing in subsequent prolactin levels at end of para. 49).

"Although use of tighter binding agents is generally associated with higher prolactin levels it is a common clinical observation that there are considerable individual variations in prolactin levels induced by identical medication at a given dose." (See para. 50 at p. 16, l. 14-16.) The present invention is directed to this problem of predicting which patients will be best suited for which antipsychotic medication (para. 003 at p. 1).

The inventors have studied prolactin levels in A1+ and A1- patients treated with a variety of typical antipsychotics (Flupenthixol, Fluphenazine Decanoate, Zuclopenthixol, Haldon, Thioridazine, Thiothixene and Trufluperazine) and a variety of atypical antipsychotics (Clozapine, Olanzapine and Risperidone). The number of patients taking these various

medications and who were included in the study is described in paragraph 0052 at page 17 of the specification.

The Examiner's question about "therapeutic" levels of prolactin (see Interview Summary dated July 24, 2009) appear to have been seeking guidance in how to interpret the prolactin levels reported in Table 1 at page 21 of the specification. As stated in the preceding paragraph on page 21, hyperprolactinemia is defined using cut-off levels of 430 mU/l in men and 560 mU/l in women. Because normal prolactin levels differ for males and females, it is understandable that the variation shown in Table 1 is higher than one might expect to be useful. This is why analyses that look at multiple variables (analysis of variance and chi-square) are more helpful in evaluating the significance of the data.

The inventors' work has shown that A1+ patients, as compared to A1- patients, "have significantly higher prolactin levels when treated with a variety of antipsychotic medications", and this allelic difference in prolactin response is most dramatic for patients treated with the loose binding agent Clozapine (see Table 1 at page 21, and paragraph 0063 at page 22, lines 3-4). As noted in paragraph 0060 at page 20, lines 20-23, "when all the antipsychotics were considered together patients carrying the A1+ allele had a significant and about a 40% higher prolactin levels than patients carrying the A1- allele ($F(1,142) = 4.50$, $P = .036$)." As described in paragraph 0061 at page 21, a chi-square analysis comparing allelic status across the groups with prolactin levels in the normal range and those with hyperprolactinemia was significant ($p+0.018$). When analyzed in this manner, looking at number of patients falling into the hyperprolactinemia category, only 5% of the patients taking the low binding agents Clozapine and Olanzapine suffered from hyperprolactinemia, compared to 81% of those taking the high binding agent Risperidone.

The inventors concluded that "optimal therapeutic effect is likely to be obtained at lower doses in A1+ schizophrenics. A1- patients may require a higher dose for maximal antipsychotic effect" (page 24, lines. 6-8). The inventors' finding that atypical antipsychotics, including Clozapine, raise serum prolactin levels (especially in A1+ patients) runs counter to the hypothesis of Kapur & Seeman (2001, Am. J. Psychiatry 158:3, see "Conclusions" portion of abstract, copy provided with Amendment of October 6, 2008) that the fast dissociation of atypical antipsychotics from the D2 receptor permits an antipsychotic effect without prolactin elevation and other adverse side effects.

**A1 Allelic Status and Susceptibility to Extrapyramidal Effects (EPS)**

As demonstrated in Example 1 at pages 8-14 of the specification, allelic status of the DRD2 gene is associated with another adverse effect of antipsychotic medication, extrapyramidal syndrome (EPS). Even with the atypical antipsychotic Risperidone (atypical in that it exhibits rapid dissociation from the dopamine receptor as compared to typical antipsychotics – see specification at page 24, lines 9-11), and even at low doses, some patients experience EPS (specification at page 8, line 18, to page 9, line 2). Example 1 compared patients receiving 2-3 mg/day Risperidone (low dose) with those receiving 4-6 mg/day (high dose) and based on A1+ or A1- allelic status. The results showed a significant gene by dose interaction ($p=0.028$), as A1+ patients fared poorly (high EPS scores) with low doses of this tight binding agent.

The results presented in Example 1 support the use of the high DRD2 binding antipsychotic Risperidone with A1- patients, but not for A1+ patients.

**A1 Allelic Status and Response to SSRIs**

Allelic status of the DRD2 gene also differentiates response to a selective serotonin reuptake inhibitor (SSRI), as demonstrated in Example 3, found at pages 25-35 of the specification. More specifically, the study showed that post traumatic stress disorder (PTSD) patients with the A1 DRD2 allele showed a significant positive response to paroxetine treatment, in contrast to A1- patients. These results support the claim elements relating to A1+ genotype being indicative of a candidate for treatment with SSRIs (such as paroxetine), and A1- genotype being indicative of a candidate for treatment with alternative antidepressant.

The findings reported in Example 3 are further supported by the data presented in Example 4, at pages 35-50 of the specification. Example 4 demonstrates that A1 allelic status is also associated with comorbid depression and anxiety in PTSD patients. A1+ status is strongly associated with comorbid somatic symptoms, anxiety, social dysfunction, and depression, independent of alcohol effects (para. 0110 at p. 40, l. 7-9), and the discussion at pages 43-44 explains how differences in D2 receptors between A1+ and A1- patients are consistent with the finding of greater efficacy of SSRIs for A1+ patients.

**Significance of CPZEK and Dose**

Paragraph 0017 at page 4, lines 19-23, of the specification defines "high dose" of medication as more than the chlorpromazine equivalent per kilogram (kg) of body weight (CPZEK) of about 10. Paragraph 0019 at page 5, lines 8-10, define "low dose" as less than a

CPZEK of about 7. As is known in the art, CPZEK is a standardized measure of antipsychotic medication that allows for dose comparisons between different medications (see, e.g., Dinakur and Sobel, 1997, *Psychiatric Services* 48(1):105, copy submitted herewith). An illustration of doses is also provided at page 7, lines 1-9, which includes the examples of "low dose" for Risperidone of 2-4 mg/day for an adult human patient, and "high dose" of Risperidone as 6 mg/day or more, as well as representative dose equivalents across a number of antipsychotic medications. Information about the doses used in Example 2, expressed as CPZEK, can be found at page 17, lines 24-27.

Important to the claimed method is not only dose of antipsychotic medication, but also selection of medication. Note that, in Example 2, even treating most patients in the "low dose" range, 44% of the patients had prolactin levels in the hyperprolactinemia range (page 21, line 6). Across all medication groups, A1+ patients had 40% higher prolactin levels; and in the Clozapine group, A1+ patients had prolactin levels **twice** those of patients lacking this allele. This result supports the claimed method whereby the A1+ genotype is indicative of a candidate for treatment with low dose **low DRD2 binding atypical** antipsychotics (not just low dose of any antipsychotic medication).

As noted in the amendment dated July 24, 2007, support for the current language of claim 1 can be found in the specification at page 24, lines 6-8. Further support of the general intent of the claimed invention can be found throughout the text of Examples 1-4. All of this material was present in the provisional patent application as filed on July 8, 2003 (see page 17, lines 27-28, of the provisional application for support for the amendment to claim 1, and pages 2-52 for the Examples).

Based on the extensive examples detailing the adverse effects of high dose atypical antipsychotic treatment for A1+ patients and the comparison to the drug response of A1- patients, it would have been apparent to one skilled in the art that the claim language recited previous to the July 24, 2007 amendment contained a clerical error that was corrected by this amendment. It would have made no sense to a person skilled in the art at the time the application was filed, to be presented with a number of examples demonstrating the adverse effects of administering typical (e.g., Flupenthixol, Zuclopenthixol) or high DRD2 binding (e.g., Risperidone) antipsychotic medications to A1+ patients as intending to support claims directed to the opposite.

Accordingly, Applicants' possession of the invention as currently claimed was supported by the application as originally filed and the amendment dated July 24, 2007 does not introduce new matter. Reconsideration is respectfully requested.

## VI. Prior Art Rejections

On pages 4 – 9 of the Office Action, claims 1, 2, and 5, and new claims 7 and 8 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Suzuki et al., *Pharmacogenetics* 10(4):335-341 (2001) (hereinafter "Suzuki #1"), in view of Suzuki et al., *Am. J. Psychiatry* 158(10)1714-1716 (2001) (hereinafter "Suzuki # 2"), and Turrone et al., *Am. J. Psychiatry* 159(1):133-135 (2002).

On page 8 of the Office Action, claims 1, 2, and 5-8 are rejected as allegedly obvious over Suzuki #1, Suzuki #2, and Turrone, as applied to claims 1, 2 and 5, and further in view of Bourin et al., *CNS Drug Review* 7(1):25-47 (2001).

The Applicants respectfully traverse these rejections because the cited references fail to teach or suggest all elements of Applicants' claimed invention. Accordingly, the rejection under 35 U.S.C. § 103(a) should be reconsidered and withdrawn.

### A. The Claimed Invention

Claim 1 recites a method of identifying a candidate psychiatric patient for treatment with atypical antipsychotic or antidepressant medication that acts at a D2 dopamine receptor (DRD2) or influences D2 dopamine receptor density. The preamble of claim 1 recites "atypical antipsychotic or antidepressant" medication, as the invention relates to the challenge of prescribing this class of medications, given the variability in their binding strength and in patient response (see para. 0049 at p. 16 of specification). The method comprises determining the patient's DRD2 genotype at the Taq1A allele by genotyping a specimen obtained from the patient.

Claim 1 specifies that A1+ patients are candidates for treatment with low dose low DRD2 binding **atypical** antipsychotics and/or SSRIs. A1- patients are candidates for treatment with high dose D2 dopamine receptor binding antipsychotics or alternative antidepressant. This method of identifying candidate patients is based on a variety of studies performed by the inventors and reported in the Examples portion of the specification. Example 1 (pp. 8-14) demonstrates the relationship between A1 allelic status and susceptibility to extrapyramidal effects in response to treatment with the atypical, high binding medication Risperidone.

Example 2 (pp. 14-24) shows that A1+ patients treated with the low binding atypical antipsychotic Clozapine are more susceptible to hyperprolactinemia. Example 3 (pp. 25-35) shows that A1+ patients suffering from PTSD respond well to the SSRI paroxetine, while A1- patients often had adverse reactions to this medication. Example 4 (pp. 35-50) shows comorbid psychopathology in PTSD with A1+ combat veterans.

The claimed invention is therefore based on a wealth of new information provided by the inventors' studies described in Examples 1-4. This new information establishes that A1+ allelic status is associated with greater adverse effects when treated with high dose or high binding atypical antipsychotics (Examples 1 & 2) and with therapeutic efficacy when treated with SSRIs (Example 3). A1- patients were shown to respond better to higher doses (or tighter-binding) of DRD2 binding antipsychotics and to fail to show a reduction in symptoms upon SSRI treatment.

### B. The Cited References Do Not Teach or Suggest the Claimed Invention

The Suzuki #1 and #2 references cited in the Office Action do not teach a method of identifying a candidate psychiatric patient for treatment with **atypical** antipsychotic or antidepressant medication. As noted in the Office Action at page 7, the medication used in the Suzuki references, nemonapride, is a **typical** antipsychotic that binds highly with DRD2 (Seeman, 2002, W. Can. J. Psychiatry, 47(1):29-35, see Table 1 at p. 34; of record per Information Disclosure Statement filed September 6, 2006). In fact, the Office Action (at page 7) states that Suzuki #1 teaches that nemonapride is substantially more effective in treating A1+ patients than A1- patients. Thus, Suzuki actually teaches away from the claimed invention.

As acknowledged in Applicants' specification (para. 0050 at p. 16), it was previously known that the typical antipsychotic nemonapride is associated with significantly elevated prolactin in A1+ female schizophrenic patients. It was not known prior to Applicants' studies, however, whether there was an association between A1 allelic status and response to the wide variety of antipsychotic agents as well as to SSRIs, and whether any such association would be found independent of gender. The results of these studies could not be predicted, given the variety of patient responses to identical medication at a given dose, the variety of DRD2 binding affinities of the various atypical antipsychotics, and the lack of correlation between prolactin levels and D2 occupancy (see, for example, "Introduction" section of Example 2, at pages 15-17 of specification).

The teachings of Turrone and/or Bourin do not compensate for the gap between the teachings of Suzuki #1 & #2 and Applicants' claimed invention. Turrone, by providing data on prolactin levels of 18 male patients of unknown genotype in response to various atypical

antipsychotic medications, does not provide guidance to the skilled artisan on determining which patients would be candidates for low dose treatment and which could be well-served by high dose treatment, nor can the teachings of the Suzuki references provide the missing guidance. Bourin, describing paroxetine as an SSRI that lacks affinity for D2 dopamine receptors, does not address the identification of which patients would be candidates for SSRI treatment as a function of Taq1A allelic status.

The combination of these references teaches that female A1+ patients respond better to the typical antipsychotic nemonapride and are at greater risk than A1- patients of neuroleptic malignant syndrome with this treatment (Suzuki #1 & #2), that a small sample of male patients of unknown A1 genotype show higher levels of prolactin in response to Risperidone as compared to other atypical antipsychotic medications, and that paroxetine does not bind D2 dopamine receptors. This combination of information does not provide the skilled person with the motivation or guidance to identify which patients will benefit from low dose treatment with low DRD2 binding atypical antipsychotics or SSRIs, and which will benefit from high dose antipsychotic or alternative antidepressant medication.

Accordingly, the rejection of claims 1, 2, 5 and 6 as obvious over the cited references is improper and withdrawal of this rejection is respectfully requested.

## VII. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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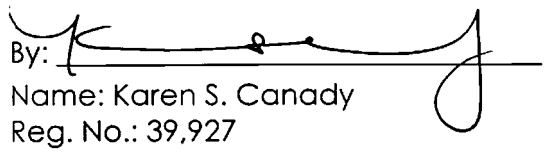
By: 
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